

## Colorectal endometriosis and pregnancy wish: why doing primary surgery

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### 1. ABSTRACT

One of the most interesting debates surrounding deep endometriosis concerns the management of patients with colorectal lesions and pregnancy intention, for which no strong first level of evidence data exists to recommend performing surgical excision of colorectal endometriosis or ART. Studies assessing the policy of primary IVF have recorded pregnancy rates inferior to 45% and estimated cumulative pregnancy rates after up to 3 cycles or IVF as high as 68%. Other authors have reported pregnancy rates over 60% in patients undergoing primary surgery for colorectal endometriosis, with spontaneous conception representing up to 60% of pregnancies. Although overall pregnancy rates appear roughly comparable in patients undergoing either IVF followed by surgery or surgery followed if required by IVF, questions remain as to whether delaying surgery for months or years impairs health. Delaying surgery may lead to bowel occlusion, higher rates of radical colorectal procedures, increased postoperative morbidity and prolonged painful complaints. To provide definitive answers requires a randomized trial on an international scale with a sample size exceeding 400 patients and follow up averaging 4 years.

### 2. INTRODUCTION

Presently one of the most exciting debates in endometriosis field concerns the management of

patients presenting with colorectal deep infiltrating endometriosis (DIE) and pregnancy intention. Colorectal DIE is a severe type of endometriosis often associated with various pelvic localizations of the disease (ovaries, fallopian tubes, Douglas pouch) that negatively impact fertility. As a majority of patients with colorectal DIE are ASFr classified in the 4<sup>th</sup> stage of the disease (1), and shown or supposed infertile. For these reasons and with the aim of assuring the best pregnancy rate (PR), ART is often proposed before colorectal DIE surgery.

### 3. PRIMARY SURGERY OR PRIMARY ART?

Recent guidelines stated that no randomized controlled trial has specifically attempted to answer this question (2,3). The effectiveness of surgical excision of deep nodular lesions prior to ART in women with endometriosis-associated infertility is not well established with regard to reproductive outcomes (2). A statement reiterated by ESHRE guidelines when referring to surgical excision of colorectal DIE. Patients however, may request surgical treatment due to pain issues.

The World Endometriosis Society consensus on current management of endometriosis noted that the best surgical approach for deep endometriosis in women with infertility is unclear. Although IVF may be less effective

for endometriosis than for other causes of infertility, it should be considered to improve the success rate above expectant management. They also highlight the risk of reducing ovarian reserve after ovarian endometrioma cystectomy (3).

The same therefore applies to patients with colorectal DIE and pregnancy desire. There is no evidence, for or against recommending performing surgical excision of colorectal DIE prior to ART to improve fertility. In these next paragraphs, we will analyze studies that focus specifically on patients with colorectal DIE and pregnancy intention, and compare overall results provided by primary ART vs. primary surgery.

### 4. SYSTEMATIC ART BEFORE SURGERY

Primary IVF is often proposed instead of surgery, to specifically shorten delay in conception and to avoid risk of postoperative ovarian reserve impairment and the negative impact of potential postoperative complications on patient fertility. Most of the related data comes from recent research by the Tenon Hospital surgical team (Paris, France) (Table 1).

Ballester *et al* (4) estimated the cumulative pregnancy rate (CPR) following 1 to 5 IVF cycles in a series of 103 patients presenting with endometriomas. Among them, 73 patients had associated DIE, with (n=43) or without (n=30) colorectal involvement. The study did not provide specific data in patients with only colorectal DIE. CPR was 69.4% in patients with DIE vs. 82.5% in women free of DIE. Despite high CPR values, only 35 patients with DIE (48%) ultimately conceived. One year after, the same surgical team reported a PR of 33% after the first cycle of ICSI-IVF in 67 patients with DIE, with or without colorectal involvement (5).

Mathieu d'Argent *et al.* (6) found that the PR in ICSI-IVF for patients with colorectal DIE involving the rectum was comparable to that of patients with tubal or male infertility. In 29 patients with colorectal DIE, the authors recorded 29 starting cycles, 24 transfer of embryos (83%), 12 pregnancies (41%) and 8 deliveries.

In a multicentric study enrolling 75 patients with colorectal DIE, Ballester *et al* (7) estimated that the CPR after 3 cycles of IVF-ICSI would reach 68.6% (95%CI 40-83.6%). The estimation was higher for women with normal AMH values (62.7% of cases) and without adenomyosis (prevalence at 28%). 68% of women had ovarian endometriomas. Despite high CPR values only 32 patients actually became pregnant during follow-up (42.7%).

Although estimated CPR values were usually over 60%, less than 45% of patients with colorectal DIE conceived during follow up. In the following paragraphs PR in primary surgery followed by ART where required,

appears higher, and furthermore spontaneous pregnancy rate is logically higher.

### 5. SURGERY FOR COLORECTAL ENDOMETRIOSIS, FOLLOWED BY ART IF REQUIRED

In a recent review (8) of series of patients presenting with bowel involvement, exclusively managed by colorectal resection (n=1320), postoperative spontaneous PR was 28.6% (95% CI = 25-32,3) and overall postoperative PR was 46.9% (95% CI = 42.9-50.9). The rate of associated ovarian endometriomas was variable through several series.

In the prospective trial of Meuleman *et al* (9), patients having undergone colorectal resection for DIE had an overall PR of 50% (27/54), a spontaneous conception rate of 24% (13/54) and an ART induced conception rate of 26% (14/54). Associated ovarian endometriomas were treated in 60% of cases on average (9).

There is some controversy as to whether removing DIE before IVF improves PR. Darai *et al.* (10) suggested that colorectal resection for DIE enhanced fertility outcomes in patients with prior IVF failure. In a randomized trial, which aimed to compare laparoscopic route to open surgery for colorectal resection in DIE, 28 patients wished to conceive after surgery, of which eleven became pregnant (39.5%), and no spontaneous conception was recorded in women managed by open surgery. Of 6 patients with preoperative ART failure, two spontaneous pregnancies were recorded and one following ART.

Stepniewska *et al.* (11) compared fertility outcomes between three groups of patients. The first two groups included patients with colorectal DIE who either accepted colorectal resection (Group A) or not (Group B). Patients managed by shaving or disc excision were excluded. There were respectively 48 and 39 patients who tried to conceive after surgery in each group. Higher spontaneous and ART-induced PR were observed in group A. Patients in group A were more likely to present with advanced rectosigmoid endometriosis responsible for stenosis, while the rate of patients having undergone cystectomy for ovarian endometriosis was comparable (56% vs. 60%). Even though the mean follow up exceeded 2 years, the rates of spontaneous (25 vs. 17.9%), ART induced (IVF and IU, 10.4 vs. 2.6%) and overall PR (35.4 vs. 20.5%) are rather low, probably owing to confounding factors unmentioned in the paper (length of period of postoperative medical amenorrhea, additional infertility factors, rate of patients with postoperative impairment of ovarian reserve). In a series of 113 infertile patients with colorectal DIE, the same surgical team recorded an overall postoperative pregnancy rate was 41.6%, with 80% of pregnancies following ART (12).

**Table 1.** Data concerning pregnancy rates following respectively primary IVF or primary surgery in patients with colorectal endometriosis

| Reference       | Study's sample | Number of patients with CRDIE trying to conceive | Number of patients with OE and technique used to manage them | Number of women shown to be infertile | Design        | Surgical approach                    | ART                    | Overall pregnancy rate observed during follow up % (95%CI) | Spontaneous pregnancy rate % (95%CI) | ART pregnancy rate % (95%CI) | Estimated cumulative pregnancy rate % (95%CI)              |
|-----------------|----------------|--|--|---------------------------------------|---------------|--------------------------------------|------------------------|--|--------------------------------------|------------------------------|--|
| Primary IVF     |                |  |  |                                       |               |                                      |                        |  |                                      |                              |  |
| 4               | 103 OE         | 43   | 43   | 43                                    | Retrospective |                                      | 1-5 IVF cycles         | 48 (DIE)   |                                      | 48 (DIE)                     | 69.4 after 4 cycles (DIE)                                  |
| 5               | 67 DIE         | NA   | 67   | 67                                    | Retrospective |                                      | 1 IVF-ICSI cycles      | 51 (DIE)   |                                      | 51 (DIE)                     |  |
| 6               | 29 CRDIE       | 29   | NA   | 29                                    | Retrospective |                                      | 29 IVF cycles<br>24 ET | 41   |                                      | 41                           |  |
| 7               | 75 CRDIE       | 75   | 51   | 75                                    | Prospective   |                                      | 1-3 IVF cycles         | 42.7   |                                      | 42.7                         | 68.6 (40-83.6) after 3 cycles                              |
| 8               | 114 CRDIE      | 114  | NA   | 114                                   | Review        |                                      |                        | 29   |                                      | 29                           |  |
| 15              | 105 DIE        | 105  | NA   | 105                                   | Prospective   |                                      | 1.6±0.8                | 24   |                                      | 24                           |  |
| Primary surgery |                |  |  |                                       |               |                                      |                        |  |                                      |                              |  |
| 8               | 597 CRDIE      | 597  | NA   | NA                                    | Review        | 597 CRR                              | Various ART            | 46.9 (42.9-50.9)   | 28.6 (25-32.3)                       | 25.5 (21.4-29.7)             |  |
| 9               | 203            | 54   | 45 LOE <sup>1</sup><br>42 ROE <sup>1</sup>                   | 54                                    | Prospective   | 76 CRR                               | Various ART            | 50   | 24                                   | 26                           |  |
| 10              | 28 CRDIE       | 28   | NA   | 15                                    | Prospective   | 28 CRR                               | Various ART            | 39.3   | 21.4                                 | 17.9                         | 45.1   |
| 11              | 48 CRDIE       | 48   | 33 CYS   | 48                                    | Prospective   | 48 CRR                               |                        | 35.4   | 25                                   | 10.4                         |  |
| 15              | 64 DIE         | 19   | 29 CYS   | 64                                    | Retrospective |                                      | 1.9±1.3 IVF            | 41   |                                      | 41                           |  |
| 13              | 52 CRDIE       | 38   | 38 PLA   | 24                                    | Prospective   | 10 CRR<br>38 Conservative procedures | Various ART            | 65.8   | 39.5                                 | 26.3                         | 63.2 (47.6-78.8) after 2 ys<br>76.3 (56.9-91.5) after 3 ys |
| 12              | 113 CRDIE      | 113  | NA   | 113                                   | Retrospective | 113 CRR                              | Various ART            | 41.6 <sup>2</sup>  |                                      |                              |  |

NA: unspecified; ART: assisted reproductive techniques; DIE: deep infiltrating endometriosis; CRDIE: colorectal deep infiltrating endometriosis; OE: ovarian endometriomas; ET: embryos transfer; CPR: cumulative pregnancy rate; CRR: colorectal resection; LPS: laparoscopic route; OR: open route; CYS: cystectomy; PLA: ablation using plasma energy; LO: left ovarian endometrioma; RO: right ovarian endometrioma; <sup>1</sup>: ovarian endometriomas were managed using various techniques; <sup>2</sup>: 64 pregnancies were recorded in 47 patients (41.6%); 20% were spontaneous and 80% followed ART

In a recent study of 124 patients managed for ovarian endometriomas by ablation using plasma energy, 52 patients had associated colorectal DIE managed by either conservative surgery or colorectal resection (13). Of the 38 patients with colorectal DIE who tried to conceive after surgery, 25 became pregnant (65.8%), giving a CPR at 2 years of 63.2% (95%CI 47.6-78.7%). Spontaneous PR was 39.5% and ART-induced PR was 26.3%. The excess in observed pregnancies may be linked to two apparent patient specificities; ovarian endometrioma ablation using plasma energy in all cases, and the high rate of colorectal conservative surgery (73.1%). The comparison between pregnancy rate in respectively patients with endometriomas (N=72) and those with both endometriomas and colorectal DIE (n=52) did not reveal statistically significant differences. The only independent risk factor decreasing PR was patient age over 35. Our study suggested that concomitant management of colorectal endometriosis does not impair risk of recurrences or the probability of pregnancy in women having benefited from ovarian endometrioma ablation using plasma energy.

In a recent systematic review, Vercellini *et al* (14) reviewed published series of patients managed for rectovaginal DIE. In patients shown to be infertile who conceived spontaneously after surgery, the mean postoperative spontaneous PR was 24% (range 10 to 41%). In our study (13), in the subgroup of women with colorectal DIE and preoperative infertility, spontaneous postoperative PR was 37.5%. The results suggest that in infertile women, surgery could render ART unnecessary in one patient out of three. The policy of systematic IVF before surgery should therefore be based on a demonstration that primary surgery reduces the rate of successful IVF by at least 24%, thus balancing out the excess in spontaneous pregnancies. To date, this demonstration has not been provided.

### 6. PRIMARY IVF VERSUS PRIMARY SURGERY: SPARSE DATA

Direct comparison of studies enrolling patients with either surgery or primary IVF would obviously be flawed by a myriad of confounding factors which reasonably impact PR; notably associated ovarian endometriomas and the technique used to treat them, previous ovarian cystectomy, associated adenomyosis, length of follow up, the postoperative length of time used for spontaneous conception, patients lost from follow up, patients who cannot afford ART costs, the severity of colorectal DIE and the technique used to treat it and complications related either to frozen pelvis IVF or colorectal DIE surgery.

To date, there is only one prospective study comparing pregnancy rates for patients undergoing either primary ART or primary DIE surgery (15), in which there was no randomization, as patients were free to choose

their management. Among 64 patients who underwent surgery, 19 had colorectal DIE (29.7%). As PR was significantly higher in the surgical arm, 41% vs. 24%, the authors concluded that extensive laparoscopic excision of DIE improves IVF pregnancy rate in women with infertility.

Caution should however be taken before extrapolating the results of the study. Most patients enrolled in both arms did not undergo more than 2 IVF procedures ( $1.6 \pm 0.8$  in 105 patients of the ART arm vs.  $1.9 \pm 1.3$  in 64 patients of the surgical arm). As the rate of success after 2 procedures varies between 50% and 60%, this may explain the rate of pregnancies in the IVF arm which are significantly lower than those reported by Ballester *et al* (4). Women who spontaneously conceived were excluded from the study, as were those who declined postoperative IVF. Thus, the results of the study are reasonably different from those that would be provided by an "intention to treat" study where all pregnancies would have been taken into account. To calculate the total rate of pregnancies, the number of patients who spontaneously conceived in each arm of the trial should be considered. There were 10 patients with spontaneous conception out of 115 patients who chose IVF, giving a spontaneous PR of 8.7%. In the surgical arm, 18 patients out of 84 spontaneously conceived, giving a spontaneous PR 2.5 times higher (21.4%). Thus, the overall PR became 29.6% vs. 51.2% ( $P=0.03$ ). By choosing surgery, patients from Sao Paolo increased their chances to conceive by 66% during the study follow up.

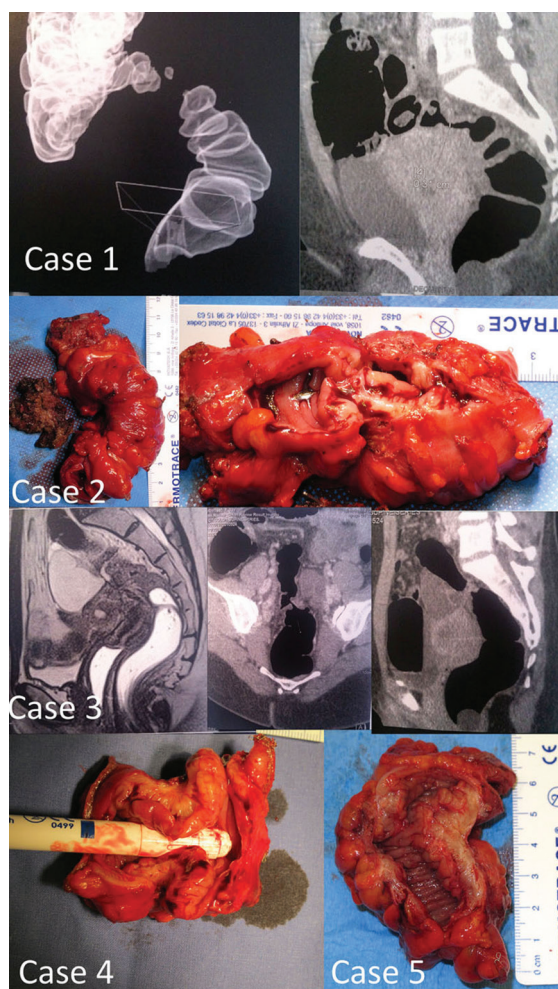
The study also reported one secondary outcome of major clinical relevance. The number of oocytes retrieval was compared between 105 women managed by IVF ( $10 \pm 5$ ), 35 women having undergone removal of DIE ( $10 \pm 4$ ), and 29 women having benefited from both endometrioma cystectomy and DIE removal ( $7 \pm 4$ ). The comparison suggested that the negative impact of surgery on ovarian reserve is likely linked to the ovarian cystectomy.

The patients enrolled in the surgical arm had a longer period of infertility and a higher number of previous failed IVF, and these factors could influence patient informed choice. On the basis of these differences, in addition to the lack of an "intention to treat" design, the study of Bianchi *et al* cannot provide a consistent answer to the question.

### 7. DELAYING SURGERY FOR COLORECTAL ENDOMETRIOSIS...IS IT ALWAYS SAFE?

Colorectal DIE is a severe, aggressive and chronic disease. Despite a shortfall in epidemiological studies focusing on spontaneous natural evolution of deep endometriosis, it is clear that patients undergoing colorectal resection for deep endometriosis at 30 years old would have not benefited from the same surgical procedure if they had been treated several years before.





**Figure 1.** MRI, computed tomography-based virtual colonoscopy and rectal specimen in 5 patients operated for colorectal occlusion or subocclusion occurring during their infertility management by ART.

To the author's knowledge, there are no publications reporting colorectal resection for deep infiltrating endometriosis in adolescents, while there are a myriad for women over 30. As the DIE nodules develop progressively over years, it is unreasonable to suppose that their growth would spontaneously stop from the point of diagnosis.

In daily practice, only a few patients benefit from thorough DIE assessment before undergoing primary IVF for infertility. For this reason, patients with colorectal DIE benefiting from ART may present unfavorable outcomes related to lesion growth during the period of time where assisted conception is attempted.

### 7.1. Bowel stenosis progression to occlusive complaints

In 2007 we reported the laborious surgical management and complications concerning a 34 years nullipara who was managed for rectal occlusion, shortly

occurring after the arrest of the contraceptive pill (16). Far from being a one-off experience, from January 2012 to July 2014 we managed 10 other patients for bowel occlusion or subocclusion due to DIE, representing 5% of 201 patients treated for colorectal DIE during this period. Among them, five young patients were treated for infertility, and bowel obstruction occurred before or after IVF procedures (Figure 1).

Anaf *et al* described 4 cases of sigmoid occlusion occurring during ovarian stimulation in patients undergoing IVF (17) and drew clinician attention to this severe digestive complication. They suggested that early diagnosis of DIE may help patients avoid months of morbidity falsely attributed to ovarian stimulation side effects.

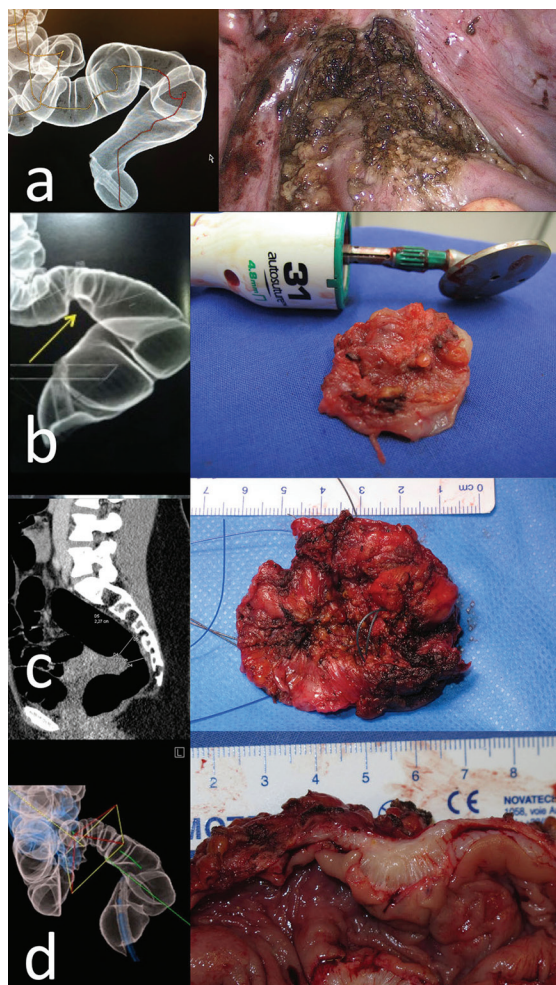
The real incidence of bowel occlusion may be flawed by publication bias. Cases of bowel occlusion due to DIE are probably underreported in the literature (18). Patients experiencing bowel occlusion are logically managed in a nearby general surgery department and are often subsequently absent from tertiary referral center databases. Two out of 10 patients in our series were first managed elsewhere for bowel resection and discontinuous stoma, and were later referred to our department due to residual DIE localizations.

### 7.2. Increase in area of the bowel involved

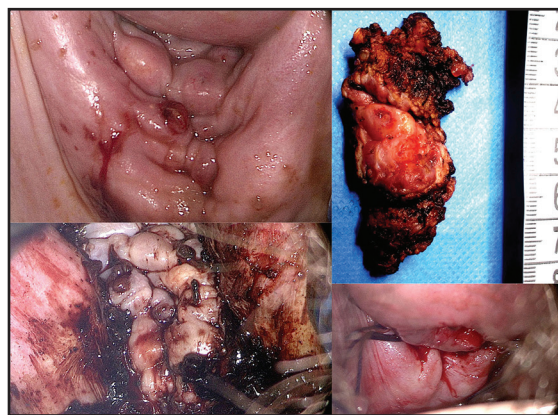
Delaying surgery may lead to increase in area of the rectal wall infiltrated by the nodule. This is of major significance for those surgeons who systematically attempt to conserve the rectum by rectal shaving or disc excisions, to reduce risk of postoperative bowel functional outcomes (1). The feasibility of conservative techniques becomes challenging in large colorectal lesions. Depth of shaving is difficult to control in large infiltrations of the rectum (19), and the surgeon limits removing fibrous tissue up to the submucosa due to risk of postoperative fistula. Disc excision using the transanal end-to-end circular staplers is not feasible in large colorectal nodules, as the stapler cannot accommodate a volume of tissue exceeding 7 cmc (20,21). Disc excision using the transanal Contour Transtar stapler can be performed in large nodules of the lower and mid rectum, however their cranial limit must not be further than 8 cm from the anus (22). Consequently, the larger the area of rectal wall infiltrated by DIE, the higher the rate of colorectal resection and the higher the risk of postoperative functional morbidity (Figure 2) (1).

### 7.3. Consequences of large infiltration of the vagina

Delaying surgery may be followed by increase in the area of the vagina involved, especially in patients where infiltration is not yet associated with severe dyspareunia, and therefore leads to large resections of vaginal fornix followed by laborious repairing of large



**Figure 2.** Progressive increase of the area of the rectal wall infiltrated by the disease leads to more radical surgical procedures on the rectum: shaving (a), disc excision using transanal end-to-end circular stapler (b), transanal excision using Contour Transtar stapler (c) and colorectal resection (d).



**Figure 3.** Large infiltration of the vaginal fornix by colorectal DIE, requiring large vaginal excision followed by the insertion of the vagina on the cervix using separate stitches.

vaginal defects (Figure 3). Extensive vaginal resections may logically be associated to higher risk of injury of splanchnic nerves and nerve fibers originating from the inferior hypogastric plexus. In these cases, performing proximal identification of hypogastric nerves does not prevent postoperative bladder dysfunction, because distal transection of the pelvic plexus is mostly required for full resection of the nodule, resulting in either acute motor or acute/chronic neurogenic bladder atony (23). In addition, the repairing of large resection of vaginal fornix can be challenging, reasonably resulting in incorrect vaginal healing with an increased risk of postoperative rectovaginal fistula or residual postoperative deep dyspareunia.

#### 7.4. Infiltration of rectum and ureters

Delaying surgery provides time for DIE to infiltrate the rectal wall, thus increasing the morbidity of later surgical procedures. Patients managed for rectal endometriosis reported longer periods of pain when compared to those managed for DIE without rectal infiltration (24), suggesting that rectal infiltration usually occurs in a secondary stage of DIE development. No randomized trial is necessary to understand that removing DIE without rectal involvement reduces the risk of rectal suture leakage, postoperative bowel dysfunction due to rectal resection, rectovaginal fistula or pelvic abscess.

Lateral progression of DIE may lead to progressive painless involvement and stenosis of the ureters. Ureteral involvement is usually progressive and symptomless (25), and becomes possible in patients managed for infertility, especially as they are free of hormonal treatment and require ovarian stimulation. Studies suggest DIE may strangle the ureter before infiltrating it, as less than 50% of patients undergoing resections of ureters had actual infiltration of ureter wall layers (intrinsic ureteral endometriosis) (26,27). This observation lends support for not delaying DIE surgery.

#### 7.5. Unnecessary prolongation of pain

The length of time necessary to plan and perform one or more IVF procedures varies among different ART centers, however it is rarely under 6 to 9 months. When primary IVF is recommended, suppressive hormonal therapy is usually stopped leading to an increase in painful symptoms related to endometriosis.

### 8. OVARIAN ENDOMETRIOMAS AND ADENOMYOSIS: TWO MAJOR CONFOUNDING FACTORS

Colorectal DIE is frequently associated with ovarian endometriomas (28). The relationship between ovarian endometriomas and infertility, is too complex to be thoroughly treated in this manuscript. It has been shown that ovarian endometriomas do not usually appear to reduce the rate of successful IVF, while



performing cystectomy before IVF significantly impairs it (2). On the other hand, large endometriomas may hamper the procedure of oocyte retrieval. The best surgical management of endometriomas remains to be established. When compared to cystectomy, ablation using bipolar current provides lower PR (29,30). Ablation using CO<sub>2</sub> laser (31) or plasma energy (32) appears to be comparable. However, removing colorectal DIE does not necessitate treating ovarian endometriomas by cystectomy during the same procedure, especially in patients with impaired ovarian reserve, bilateral endometriomas or antecedents of cystectomy. In a recent study, we observed that surgical management of colorectal endometriosis does not negatively impact PR in patients with ovarian endometriomas (13). Based on these findings delaying colorectal DIE surgery in patients intending to get pregnant becomes a disputable decision.

Adenomyosis is frequently associated with colorectal endometriosis, so that in many cases large posterior adenomyomas appear to impact the digestive tract (33) with several authors highlighting the negative impact of adenomyosis on PR, both spontaneous and ART induced (34-36). However, accurate diagnosis of adenomyosis may be difficult, especially in young patients, as surgeons and radiologists use different criteria to affirm it.

The frequent presence of ovarian endometriomas and adenomyosis most likely flaws direct comparison of fertility outcomes reported in various series, as for outcomes of prospective trials where the strategy employed depends on patient informed choice. Patients with severe adenomyosis, low ovarian reserve or multiple endometriomas will be more frequently enrolled in the primary IVF arm than in that of surgery. To control the impact of associated confounding factors, either hidden or obvious, a randomized design provides the solution.

### 9. FURTHER RANDOMIZED CONTROLLED TRIALS: GOALS AND OUTCOMES

There is a major need for a large randomized controlled trial, in which the design focuses both on overall PR and general health of women: rate of pre- and post treatment complications and unfavorable outcomes, quality of colorectal function, rate of conservative colorectal surgery, spontaneous PR and overall treatment costs.

This trial should enroll patients from 18 to 40 years with colorectal DIE and immediate pregnancy intention. Excluded should be patients aged over 40, multipara with no pregnancy intention, young patients with no immediate pregnancy intention, homosexual patients not considering spontaneous conception and patients with severe disease requiring immediate surgery

(advanced colorectal stenosis, hydronephrosis, severe deep dyspareunia). Eligible women would therefore represent up to 50 to 60% of patients with colorectal DIE.

The patients should be randomly assigned to either “ART” or “Surgery” groups. To maximize the chances of conception using ART, the patients enrolled in the “ART” arm would undergo up to 3 cycles of IVF, before planning surgery, the latter being considered in cases where the 3<sup>rd</sup> consecutive IVF is unsuccessful. When patients conceive by IVF, surgery would be proposed post delivery. Patients enrolled in the “Surgery” arm should benefit from surgery followed if required by up to 3 cycles of IVF, with the proviso that when intraoperative data and fertility assessment suggest that spontaneous conception is likely, the patients would benefit from 9 to 12 months of spontaneous conception attempting before referral for ART.

Key to follow up would be providing information on patient capacity to conceive. A period of one year would be necessary for both groups for postoperative spontaneous conception, three cycles of IVF (including pre-treatment assessment) may require up to 2 years and in cases of pregnancy, surgery should be postponed by at least one supplementary year. With these factors taken into account the follow up period should not be inferior to 4 years.

PR in the “ART” group could be expected to average 50% (probably lower than estimated CPR and higher than previously observed PR) (7) after IVF procedures, potentially reaching 55-60%, post surgery due to postoperative spontaneous conception. PR in the “Surgery” group may attain 70%, due to postoperative spontaneous conception (30% on average) and ART-induced pregnancies (40%). These predictions indicate that this randomized trial should compare CPR values of 55-60% vs. 70%. 176 patients are necessary in each arm to attain a statistically significant difference between 55 and 70%, with a statistical power of 80%. The number should however be increased to 200 in order to prevent deleterious impact of potential conversions from the ART to the Surgery arm or potential premature abandon of pregnancy intention. 376 patients would be required in each arm to reveal a statistically significant difference of 60 to 70%. Such a trial would need to run on an international scale, involving management of around 800 patients with colorectal DIE for the enrollment of a sample of 400 subjects. Costs to the trial promoter, over and above data management of the 4-year follow up, would include 1 to 3 IVF procedures in patients enrolled in the “ART” arm and in 60 to 70% of patients in the “Surgery” arm. The uncertain sample size (due to lack of data concerning long term PR) and the possibility that some patients would abandon the project of pregnancy during follow up present however a risk to the statistical power of the trial.

**Table 2.** Primary surgery ahead of primary assisted reproductive techniques in the management of patients with colorectal endometriosis and pregnancy wish

| Advantages   | Disadvantages   |
|--|---|
| <ul style="list-style-type: none"> <li>• High rate of postoperative spontaneous pregnancies in patients preoperatively supposed to be infertile (13-15)</li> <li>• Reduction of overall management expenses in addition to no use of ART in patients with spontaneous pregnancy (13-15)</li> <li>• Overall rate of pregnancy in patients with primary surgery at least comparable, if not better, than that recorded in patients undergoing primary IVF (8,11,15)</li> <li>• No reduction of oocyte retrieval during postoperative IVF, except where ovarian endometrioma cystectomy is associated with deep endometriosis surgery (15)</li> <li>• Pregnancy rate probably enhanced by colorectal endometriosis surgery in patients with preoperative IVF failure (10)</li> <li>• The risk of endometriosis related complications, such as bowel occlusion, rectal infiltration and ureteral stenosis, is logically avoided when surgery is performed first (16-18,24,25)</li> <li>• Conservative colorectal surgery has greater feasibility when it is performed early than when it is attempted in advanced stages of the disease which lead to large infiltrations of the digestive tract</li> <li>• Rate of postoperative complications probably lower when surgery is performed earlier than when postponed due to primary IVF</li> </ul> | <ul style="list-style-type: none"> <li>• Risk of postoperative complications, such as rectovaginal fistula or pelvic abscess, which may negatively impact spontaneous conception; furthermore, the management of postoperative complication usually delays the implementation of secondary ART</li> <li>• Risk of significant reduction in ovarian reserve, leading to definitive ovarian failure when ovarian endometrioma surgery is associated with deep endometriosis surgery (2)</li> <li>• Psychological impact of advanced colorectal surgery probably higher when performed in nullipara</li> </ul> |

Conversely, it is likely that the overall complications rate related to treatment, spontaneous PR, quality of life during follow up, overall digestive and bladder morbidity and overall expenses related to surgery and IVF would be significantly favorable to the “Surgery” arm, providing 1<sup>st</sup> level evidence data supporting primary surgery over ART. As results from such a trial will probably remain unavailable for some years, the compelling debate between defenders of surgery and those of IVF is far from closed.

## 10. CONCLUSION

Worldwide meetings on endometriosis thrive on debates around the theme of the opinion here presented, with conclusions varying significantly from one conference to another according to speaker experience and views. An absence of consensus and inevitable divergent advice leave patients routinely confused with hesitation further delaying accurate management of the disease. Data available in the literature suggest that the current policy of systematic IVF prior to surgery in patients with colorectal DIE is questionable (Table 2). This review is exclusively based on data available in the literature and specific to patients with colorectal DIE and pregnancy intention, and highlights that when PR is taken into account along with expected disease development, primary surgery followed by spontaneous conception or ART appears more suitable than primary ART. A definitive answer can be provided by a randomized trial, although sample size, length of follow up and cost may challenge feasibility. Trials providing shorter follow up and smaller sample sizes risk further blurring a topic, which requires greater clarity.

## 11. ACKNOWLEDGEMENTS

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**Abbreviations** : IVF : *in vitro* fertilisation ; ART : assisted reproductive techniques ; PR : pregnancy rate ; CPR : cumulative pregnancy rate ; DIE : deep infiltrating endometriosis

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